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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,452	07/31/2001	Sun Ai Raillard	02-107410US	4651

30560 7590 04/22/2003

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EXAMINER
HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
1652	10

DATE MAILED: 04/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/920,452	RAILLARD ET AL.	
	Examin r	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this c mmunication appears on the c ver sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *74,76-79,81 and 88-103* is/are pending in the application.

4a) Of the above claim(s) *96-103* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *74,76-79,81 and 88-95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The art unit location of your application and examiner has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1652, Examiner Richard Hutson Ph.D.

Applicants preliminary amendment of canceling claims 1-73 and 82-87, amending claims 74 and 81 and adding new claims 88-103, Paper No. 9, 3/18/2003, is acknowledged. Claims 74, 76-79, 81 and 88-103 are at issue and are present for examination.

Election/Restrictions

Applicant's election without traverse of Group III, Claims 1-7 and species C, a nucleotide analogue which is a nucleotide comprising a fluorescent label, species F, a nucleotide incorporating enzyme which is a nucleic acid polymerase, sub-species F-2 a nucleic acid polymerase which is an RNA dependent DNA polymerase, species K, identifying a nucleotide incorporating enzyme variant by spectroscopy; and species KK, a desired property which is tolerance to impurities, in Paper No. 9 is acknowledged.

Upon further consideration it has been determined that the claims should be re-restricted as follows:

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 74, 76-79, 81 and 88-95, drawn to a nucleotide incorporating enzyme variant that incorporates a non-natural or rare nucleotide

analogue at least 10% as efficiently as a naturally occurring nucleotide, classified in class 435, subclass 194.

II. Claims 96-103, drawn to a nucleotide incorporating enzyme variant that polymerizes a polynucleotide in a template dependent manner in the presence of a biological impurity found in blood, plasma or urine, classified in class 435, subclass 194.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions the nucleotide variants of Groups I and II are structurally different molecules comprising structurally different amino acid sequences which have functionally different desired properties.

Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper.

During a telephone conversation with Sharon Fujita on 4/16/2003 a provisional election was made with traverse to prosecute the invention of Group I, claims 74, 76, 77-79, 81 and 88-95. Affirmation of this election must be made by applicant in replying to this Office action. Claims 96-103 withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

Applicants statement on the first line of the specification to state that this application claims the priority of U.S. Provisional applications 60/244,7644, filed October 31, 2000 and Number 60/222,056 2 filed July 31, 2000, the disclosures of each of which is incorporated herein in their entirety for all purposes is acknowledged.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Applicants filing of information disclosure, Paper No. 3, filed 12/13/2001, is acknowledged. Those references considered have been initialed. References CJ

through CR were not found with the instant application and have therefore not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 74, 76-79, 81 and 88-95 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 77 and 78 are indefinite in that it is confusing in that each of claims 77 and 78 are drawn to the nucleotide incorporating enzyme variant of claim 74, wherein said variant incorporates nucleotides or nucleotide analogues with either low (claim 77) or high fidelity (claim 78). It is unclear as to the relationship between the ability of the claimed enzyme variant to incorporate non-natural or rare nucleotides analogue and the fidelity of the enzyme variant. As applicants specification only gives guidance with respect to "fidelity to a template" when discussing "nucleic acid polymerases" (see page 18, line 5), it is unclear as to the intended meaning of fidelity when the claimed nucleotide incorporating variant is not a nucleic acid polymerase or a naturally occurring nucleotide. Thus the meaning of fidelity and its relationship to the ability to incorporate nonnatural nucleotide analogues relative to a natural nucleotide is unclear. Further, depending on applicants intended meaning of fidelity, is it possible that the claimed

genus of nucleotide incorporating enzyme variants of claim 74 can encompass those enzymes with both low fidelity and high fidelity and if so what is the relationship between these additional characteristics of the claimed nucleotide incorporating enzyme variants?

Claim 74 (claims 76-79, 81 and 88-95 dependent on) is indefinite in that it is unclear what applicants mean or what is encompassed by the recitation "diversifying the plurality of nucleic acids".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 74, 76-79, 81 and 88-95 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 74, 76-79, 81 and 88-95 are directed to all nucleotide incorporating enzyme variants that incorporates a non-natural or rare nucleotide analogue at least 10% as efficiently as a naturally occurring nucleotide, wherein the nucleotide incorporating enzyme variant is produced by the methods specified in the claims. The specification, however, does not provide a single representative species of the claimed nucleotide incorporating enzyme variants. There is no disclosure of any particular

structure to function/activity relationship in any species. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 74, 76-79, 81 and 88-95 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a *Taq* DNA polymerase variant as taught by Brandis et al. (See 102 rejection below), does not reasonably provide enablement for any nucleotide incorporating enzyme variant that incorporates a non-natural or rare nucleotide analogue at least about 10% as efficiently as a naturally occurring nucleotide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4)

the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 74, 76-79, 81 and 88-95 are so broad as to encompass **any** nucleotide incorporating enzyme variant that incorporates **any** non-natural or rare nucleotide analogue at least about 10% as efficiently as a naturally occurring nucleotide. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of nucleotide incorporating enzyme variants and the extremely large number of non-natural or rare nucleotide analogues broadly encompassed by the claims. The claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural limits on the claimed nucleotide incorporating enzyme variants nor the non-natural or rare nucleotide analogues that the claimed variant has an increased efficiency for incorporating. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure does not teach or give any guidance whatsoever as to how to make the claimed nucleotide incorporating enzyme variants.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any nucleotide incorporating enzyme because the specification does not establish: (A) regions of the protein structure which may be modified without effecting nucleotide incorporation activity; (B) the general tolerance of nucleotide incorporating enzymes to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a nucleotide incorporating enzyme with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to result in the nucleotide incorporation activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994,

Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those polypeptides of the claimed genus having the claimed nucleotide incorporation activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any nucleotide incorporating enzyme. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical

Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 74, 76, 77-79, 81, 88-95 are rejected under 35 U.S.C. 102(e) as being anticipated by Brandis et al. (U.S. Patent No. 6,265,193 B1).

Brandis et al. DNA polymerases having improved labeled nucleotide incorporation properties. Brandis et al. specifically teach a number of Taq DNA polymerase mutants which have at least a 2 fold reduced discrimination for fluorescein-type dye labeled nucleotides as compared with naturally occurring DNA polymerases. While it is admitted that Brandis et al. do not specifically measure the efficiency of incorporation of a fluorescein-type dye labeled nucleotide relative to a natural occurring nucleotide but rather they measure the efficiency of incorporation of a fluorescein-type dye labeled dideoxynucleotide relative to a unlabeled dideoxynucleotide, based on the results shown for the generated mutant DNA polymerases (See examples 2 and 4, Tables 2 and 1) it is believed that this is an inherent property of the DNA polymerases taught by Brandis et al. Therefore claims 74, 76, 77-79, 81, 88-95 are anticipated by Brandis et al.

It is acknowledged that Brandis et al. do not produce the taught DNA polymerase mutants by the process(s) specified by applicants in the rejected claims, however the patentability of claims drawn to a nucleotide incorporating enzyme variant are not determined by the process by which the variant is made but rather by the nucleotide

incorporating enzyme variant itself and thus the variants taught by Brandis et al. anticipate the claimed variants.

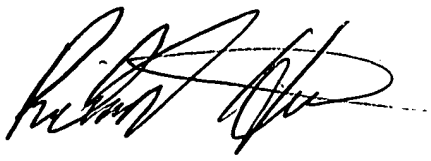
Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Richard Hutson, Ph.D.
Primary Patent Examiner
Art Unit 1652
April 17, 2003